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10/729,056	12/05/2003	David J. Grainger	295.009US4	9616

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
12/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,056	GRAINGER ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *153-155 and 157-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *153-155, 157-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 10/1/2007 amending claims 153, 154 and 169. Claim 156 has been canceled. Claims 153-155, 157-173 are pending and are being examined on the merits herein.

Response to Remarks

The rejection of claims 153-155, 157-173 under 35 U.S.C. 103(a) as being unpatentable over Grainger et al (Biochem J, 1993, 294, 109-112) in view of Nuovo et al. (Int J of Gynecological Pathology, p 125-131, 1989) and further in view of Purchio et al. (U.S. 5,221,620) is withdrawn due to the amendment of claims 153, 154 and 169. The rejection of claims 153-155, 157-159, 164, 165, 168 under 35 U.S.C. 103(a)as being unpatentable over Gylling et al. (Atherosclerosis, 96, 1992, 245-247) in view of Ellis et al. (U.S. 4,826,876) is withdrawn due to the amendment of claims 153, 154 and 169. The rejection of claims 153-155, 157-173 under 35 U.S.C. 103(a) as being unpatentable over Grainger et al (Biochem J, 1993, 294, 109-112) in view of Bjorkerud (Arteriosclerosis and Thrombosis, 1991, 11, 892-902) and further in view of Purchio et al. (U.S. 5,221,620) is withdrawn due to the amendment of claims 153, 154 and 169. The rejection of claims 153-155, 169 under 35 U.S.C. 103(a) as being unpatentable over Fischer et al. (Experimental and Molecular Pathology, 43, 288-296, 1985) in view of Grainger et al (Biochem J, 1993, 294, 109-112) and further in view of Purchio et al. (U.S. 5,221,620) is withdrawn due to the amendment of claims 153, 154 and 169. The obviousness double patenting rejection of claims 153-155, 157-173 provisionally rejected over claims 173-194, 196-203, 205-311 and 231 of the co-pending application

is maintained as the Applicants' have not filed any terminal disclosure or put forth any arguments. The obviousness double patenting rejection over U.S. Patent Nos. 5,472,985, 5,770,609, 5,599,844, 5,773,479, 5,847,007, 6,166,090, 6,197,789, 6,212,079, and 6,251,920 is withdrawn due to Applicants' filing of the Terminal Disclosure. Applicants arguments regarding the rejection of claims 153-173 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent Nos. 5,595,722, 6,074, 659, 5,559,884 have been found to be persuasive and hence the rejections are withdrawn. Applicants' arguments regarding the rejection of claims 153-159, 164, 165, 168 under 35 U.S.C. 103(a)as being unpatentable over Sawada et al. (Pharmacometrics, 1992) in view of Ellis et al. (U.S. 4,826,876) have been considered and found not persuasive. Applicants' arguments regarding the rejection of claims 153-168 under 35 U.S.C. 112, first paragraph have been considered and found not persuasive. Applicants' amendments necessitated the modified and the new rejections presented in this office action. Hence the action is made final.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided

the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 153-173 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 173-194,196-203, 205-211 and 231 of copending Application No. 09/754,775. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the method claimed in claims 153-173 of the instant application utilizes the same biological pathway comprising increasing the level of TGF-beta encompassing utilizes the same active agents in the method of claim 173 of the co-pending application. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the co-pending application and hence renders obvious over the diseases and the agents claimed in the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 153-155, 157-168 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing a vascular indication in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a therapeutic method for preventing or treating a vascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation; b) administering a cytostatic dose of the agent to the mammal so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof.

(2) Breadth of the Claims:

The instant claims are broad and embrace preventing or treating a vascular indication in a mammal which indication is characterized by a decreased lumen diameter, comprising: a) selecting an agent for TGF-beta elevation; b) administering a cytostatic dose of the agent to the mammal so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, increase plaque stability, or any combination thereof.

(3) Guidance of the Specification:

The guidance of the specification is towards the prevention of vascular indication administering TGF-beta agent is completely lacking.

(4) Working Examples:

Applicant does not provide any working examples for the prevention of vascular indication administering TGF-beta agent in a mammal.

(5) **State/predictability of the Art:**

The state of the art regarding treating a vascular indication administering TGF-beta agent in a mammal is relatively high. However, the state of the art for prevention of vascular indication administering TGF-beta agent in a mammal is underdeveloped.

(6) The Quantity of Experimentation Necessary:

The instant claims read on the prevention of vascular indication administering TGF-beta agent in a mammal. As discussed above, the specification fails to provide sufficient support for completely protecting a mammal against vascular indication. Applicant fails to provide information sufficient to practice the claimed invention, absent

undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly the claims are evaluated as a method for treating a vascular indication in a mammal and not as a method for preventing a vascular indication in a mammal.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 153-155, 157-159, 164, 165, 168 are rejected under 35 U.S.C. 103(a)as being unpatentable over Sawada et al. (Pharmacometrics, 1992) in view of Ellis et al. (U.S. 4,826,876).

Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats.

Sawada et al. do not teach a method of treatment of a mammal with cardiovascular or vascular indication (atherosclerosis) or mechanism of increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation, and dosage formulation set forth in claim 153.

Ellis et al. teach that patients having elevated plasma lipid levels are considered at risk of developing coronary heart disease or other manifestations of atherosclerosis as a result of their high plasma cholesterol concentrations. The reference further teaches that anti-hyperlipidaemic agents, which lower the ratio of LDL-cholesterol to HDL cholesterol, are indicated as anti-atherosclerotic agents (col. 17, lines 51-57).

It would have been obvious to one of ordinary skill in the art to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis. One would have been motivated to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis because Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats and Ellis teach that elevated lipid levels are considered at risk of developing coronary heart disease. One would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis. The references do not specifically teach determining an agent for TGF-beta elevation or selecting a cytostatic dose of the agent as claimed by applicant. That applicant may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol) which would result

from the claimed method upon the administration of same active agent in a same amount to the mammal in need thereof. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 153-155, 157-159, 164, 165, 168 are rejected under 35 U.S.C. 103(a)as being unpatentable over Gylling et al. (Atherosclerosis, 96, 1992, 245-247) in view of Ellis et al. (U.S. 4,826,876).

Gylling et al. teach that tamoxifen and toremifene, another synthetic antiestrogen inhibited cholesterol synthesis in animal experiments (Mantyla, Kangas, Miettinen and Nieminen, 1991, unpublished data) (p 245, col.1, lines 11-15).

The reference does not teach a method of treatment of a mammal with cardiovascular or vascular indication (atherosclerosis) or mechanism of increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation, and dosage formulation set forth in claim 153.

Ellis et al. teach that patients having elevated plasma lipid levels are considered at risk of developing coronary heart disease or other manifestations of atherosclerosis as a result of their high plasma cholesterol concentrations. The reference further teaches that anti-hyperlipidaemic agents, which lower the ratio of LDL-cholesterol to HDL cholesterol, are indicated as anti-atherosclerotic agents (col. 17, lines 51-57).

It would have been obvious to one of ordinary skill in the art to employ toremifene a synthetic antiestrogen to a mammal with cardiovascular or vascular indication such as atherosclerosis. One would have been motivated to employ toremifene to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis because Gylling teaches that toremifene inhibited cholesterol synthesis in animal experiments. Ellis teaches that elevated lipid levels are considered at risk of developing coronary heart disease. One would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis. The references do not specifically teach determining an agent for TGF-beta elevation or selecting a cytostatic dose of the agent as claimed by applicant. That applicant may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol) which would result from the claimed method upon the administration of same active agent in a same amount to the mammal in need thereof. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 153-155, 157-162, 165, 169-172 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al. (WO 94/09764) and Schilling (Therapiewoche, 1975, vol. 25, 10, 1157-1172) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and further in view of Kangas, (Breast Cancer Res Treat, 1990, Aug 16, S 3-7).

Ito et al. teach that use of nonsteroidal anti-estrogen compound such as toremifene is effective remedy for the treatment of blood vessels disease such as angitis (small vessel disease). (page 1, first two paragraphs). The reference teach the oral administration of tamoxifen analog, toremifene to mice (30 mg or 15 mg/kg)

Schilling teaches that angitis mainly affect small to average size arteries (see Abstract).

Ito et al. does not explicitly teach that toremifene elevates TGF-beta level.

Knabbe et al. teach the induction of transforming growth factor beta by the antiestrogen toremifene (See Abstract).

The references do not explicitly teach that toremifene have reduced estrogenic activity.

Kangas teach that antiestrogenicity/estrogenicity ratio of toremifene in animal models is about 5 times that of tamoxifen (See Abstract).

The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary

for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results.

Claims 153-155, 157-162, 165, 169-172 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang (U.S.Patent No. 5,445,941) in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) and further in view of Kangas, (Breast Cancer Res Treat, 1990, Aug 16, S 3-7).

Yang teaches that antiestrogen such as toremifene is useful for treating osteoporosis because it induce human fetal fibroblast to secrete TGFb in absence of estrogen receptor. (column 2, under antiestrogens, column 4, lines 6-10). Yang teaches that elevated serum levels of low density lipoproteins correlate with increased incidence of coronary artery disease, atherosclerosis and myocardial infarction are noted in women with osteoporosis.

Ito et al. does not explicitly teach that toremifene elevates TGF-beta level.

Knabbe et al. teach the induction of transforming growth factor beta by the antiestrogen toremifene (See Abstract).

The references do not explicitly teach that toremifene have reduced estrogenic activity.

Kangas teach that antiestrogenicity/estrogenicity ratio of toremifene in animal models is about 5 times that of tamoxifen (See Abstract).

The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would

routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art that the osteoporosis patients disclosed by Yang et al. is at risk of cardiovascular or vascular indication characterized by a decreased lumen diameter because a condition such as osteoporosis correlates with increased incidence of coronary artery disease, atherosclerosis and myocardial infarction as taught by Yang et al.

Claims 163 and 173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al. (WO 94/09764) and Schilling (Therapiewoche, 1975, vol. 25, 10, 1157-1172) in view of Kangas, (Breast Cancer Res Treat, 1990, Aug 16, S 3-7) and further in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) as applied to claims 153-155, 157-162, 165, 169-172 above and further in view of Warri et al. (J Natl Cancer Inst. 1993, 85, 17, 1412)

Ito et al, Schilling, Kangas and Knabbe's teachings discussed as above.

The references do not teach that the agent toremifene increases the production of TGF-beta mRNA.

Warri et al. teach that elevated TGF beta 1 mRNA was observed in vitro and in vivo grown tumor cells treated with toremifene (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention that toremifene increased or elevated the production of mRNA because of the

teachings of Warri et al. The reference teach that treatment with toremifene increased TGF beta 1 mRNA levels in vitro and in vivo grown tumor cells.

Claims 166-168 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al. (WO 94/09764) and Schilling (Therapiewoche, 1975, vol. 25, 10, 1157-1172) in view of Kangas, (Breast Cancer Res Treat, 1990, Aug 16, S 3-7) and further in view of Knabbe (Am J Clin Oncol. 1991, 14, 2, S15-20) as applied to claims 153-155, 157-162, 165, 169-172 above and further in view of Grainger et al (Biochem J, 1993, 294, 109-112).

Ito et al, Schilling, Kangas and Knabbe's teachings discussed as above.

The references do not teach that the agent toremifene decreases smooth cell proliferation and also its association with procedural vascular trauma.

Grainger et al. teach decrease in the rate of proliferation of rat vascular smooth muscle cells in culture by tamoxifen (see Abstract).

It would have been obvious to one of ordinary skill in the art that toremifene would decrease in the rate of proliferation of rat vascular smooth muscle cells because toremifene is a structural analog of tamoxifen. The compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties. The references do not teach that the smooth muscle cell proliferation is associated with procedural vascular trauma. It would have been obvious to one of

ordinary skill in the art to administer an agent in a vascular indication that is associated with procedural vascular trauma. One of ordinary skill in the art would have been motivated to administer an agent that has been shown by Grainger that decreases the proliferation of smooth muscle cells in general to any condition related to smooth muscle cell proliferation in order to achieve similar therapeutic benefits.

Claims 153-155, 169 are rejected under 35 U.S.C. 103(a)
as being unpatentable over Connolly et al. (U.S.Patent No. 5,250,561).

Connolly et al. teach that tetrahydroindazole compounds are useful in treatment or prevention of hypercholesterolemia and atherosclerosis (See Abstract).

The references do not explicitly teach selecting a cytostatic dose of the agent as claimed by applicant. The dosage or selection of an agent or mode of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. The instantly claimed "an agent" to be employed is encompassed by this teaching because the tetrahydroindazole compound disclosed by Connolly et al. has no estrogenic activity which meets the requirement of the agent having reduced estrogenic activity relative to tamoxifen. Further, the mechanism of action of increasing the level of TGF-beta gives the pharmacological effect does not alter the fact that the compound (an agent having property of reduced estrogenic activity relative to tamoxifen) has been previously used to obtain the same

pharmacological effects (atherosclerosis) which would result from the claimed method. The patient, condition to be treated and the effect are the same. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims. It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered tetrahydroindazole compounds in the treatment of vascular disorders because Connolly teach tetrahydroindazole compounds are useful in treatment or prevention of hypercholesterolemia and atherosclerosis, One of ordinary skill in the art would have been motivated to administer tetrahydroindazole compounds to inhibit lipid accumulation or increase plaque stability in expected success because Connolly teach the compounds are useful in the treatment of hypercholesterolemia and atherosclerosis.

Response to Arguments

Applicants' arguments regarding the rejection of claims 153-168 under U.S.C 112(1) paragraph have been considered and found not responsive. In response, these arguments are not convincing because prevention requires the recited method to be completely effective in all patients at all times. Applicants' argue that data shown in example 7 demonstrates that adult mice administered with tamoxifen reduced the number and size of lesions. However, it does not appear that administration of tamoxifen or a TGF-beta elevating compound that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen would work 100% of the time in 100% of the patients. The data supports for the reduction in number and size of lesions but not prevention of vascular disorders. Therefore, it is reasonable that a skilled artisan would

not accept without question that applicant's claimed method would work as recited, and as such undue experimentation is required before a skilled artisan can practice the full scope of applicant's recited methods with respect to prevention of vascular indication or disorders. "Prevention" is defined in Webster's New World Dictionary as "to keep from happening; make impossible by prior action." See Webster's New World Dictionary, 3rd College Ed., Webster's New World Dictionary Publishing, page 1067 - 1068 (1988). There is nothing of record to provide support that the claimed method "makes impossible" the occurrence of vascular disorders in a given patient upon administration of agents that elevate TGF-beta. Applicant is advised that although claim language, such as "preventing" or "curing" lack enablement under 35 U.S.C. § 112, first paragraph, phrases such as "reducing the incidence," "reducing the frequency," or "reducing the likelihood," etc. are considered by the Office to be enabling, assuming of course that the specification in question has adequate written description and support for the asserted and claimed utility.

Applicants argue that based upon the disclosure of Sawada, it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGFb levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. This is not persuasive because the teaching of Sawada is clear that the effect of decrease in total cholesterol is resulted of orally administered NK622 (toremifene). Applicants' attention is drawn to second paragraph of abstract of Sawada where it states "This experiment yielded the following results.., showed decreases in

total cholesterol, phospholipid and total protein values in rats receiving 0.1 mg/kg or more...".

Conclusion

Applicant's amendment necessitated the modified and new rejections presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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